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10/518,405	11/18/2005	Motonori Miyakawa	Q85416	8028

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EXAMINER
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GALLIS, DAVID E

ART UNIT	PAPER NUMBER
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1609

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06/11/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

10/518,405

Applicant(s)

MIYAKAWA ET AL.

Examiner

David E. Gallis

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 15 March 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-6 and 11-13 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 11-13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☒ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 12/17/04.
- 4) ☒ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_.

**DETAILED ACTION**

1. Claims 1 through 6 and 11 through 13 are pending. Claim 6 has been amended. Claim 2 has been withdrawn. Claims 7 through 10 have been cancelled.

The Applicant states the instant application to be the National Stage of Application No. PCT/JP03/07799 filed June 19, 2003. As such, all conditions pursuant to 35 U.S.C. 119(a-d) have been met for the foreign priority date of June 19, 2002 provided by application JP 179088/2002.

On the basis of the Examiner's May 15 and 16, 2007 telephone discussions with Applicant's representative, the Examiner understands that Group IV is the elected Invention for examination and that Applicant understands that Group IV is defined to contain moiety Y as  $-C(CH_3)_2-CH_2-$ . As noted in Applicant's March 15, 2007 response to the election requirement, the Examiner acknowledges that the correct term defining the number of ring carbons fused to the tetrahydroquinoline core is "m" rather than "n" and that the Examiner stands corrected.

***Election/Restrictions***

2. Applicant's election with traverse of Group IV with the selection of substituent Z as heteroaryl, is acknowledged by the examiner. The technical feature linking Groups I through IX lacks novelty as a tetrahydroquinoline derivative. Hayes et al. teach a tetrahydroquinoline derivative wherein with respect to the instant formula (I)  $R^1=NO_2$  or CN,  $R^2=H$ ,  $X=CH$ ,  $m=0$  and the  $Y-N(R^9)[(CO)Z]$  equivalent is  $C_2-C_{10}$  substituted alkyl (See Hayes et al, US 5,925,527, 20 July 1999, columns 3 and 4.) Likewise, both the Examiner's STN search and the International Search Report uncovered Hanada et al.,

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as a common reference of interest. Hanada et al. additionally provides relevant art for instant formula (I) substituent and component options, with the exception of the heteroaryl Z group option which is integral to the elected Group IV subject matter. Hanada et al., also teaches an instant formula (I) structure where Z is t-butoxycarbonyl (see column 18, Table 3, Example 26). This demonstrates lack of novelty with respect to the compound claimed, and therefore the restriction requirement is proper and made final.

The Examiner has withdrawn claim 2 from consideration since it is no longer operable or relevant with respect to the elected Group IV subject matter.

The functional group options of formula (I) that characterize the elected Group IV are as follows:

R<sup>1</sup> is a cyano group;  
R<sup>2</sup> is hydrogen;  
X is CH;  
Y is -C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>-;  
Z is substituted or unsubstituted heteroaryl; and  
m is 0.

Subject matter in claims 1 and 3 through 6 that does not read on the above subject matter is withdrawn for consideration for the purpose of this examination.

The compounds of formula (I) that exemplify the elected Group IV are examples 100 through 112 of the instant disclosure.

Hanada et al. additionally teach a tetrahydroquinoline derivative wherein with respect to the instant formula (I) R<sup>1</sup>=NO<sub>2</sub> or CN, R<sup>2</sup>=H, X=CH, m=0 and the Y-N(R<sup>9</sup>)[(CO)Z] equivalent is alkyl substituted alkylene-NH-C(O)-aryl (see Hanada et al., WO01/27086, Pub 4/19/2001 or US 7,037,919 B1, column 3, line 32 through column 4,

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line 37). This clearly reads on the electable species wherein Z = phenyl and thereby limits the species election to Z = heteroaryl.

The examiner grants the rejoining of amended claim 6 drawn to a composition of the elected Group IV compounds and pharmaceutically acceptable carrier or excipient, and claims 11 through 13 drawn to methods of prevention and treatment with same compounds. Claims 6, and 11 through 13 are hereby rejoined and fully examined for patentability under 37 CFR 1.104 as restricted to the elected Group IV subject matter.

Because claim 6, and 11 through 13 previously withdrawn from consideration have been rejoined, the restriction requirement with respect to Groups VIII and IX as set forth in the Office action mailed on February 13, 2007 is hereby withdrawn. In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

### ***Double Patenting***

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

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from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1 and 3 through 6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/522,553 (US 2005/0277660) in view of Hanada et al., (US 7,037,919). Copending claim 1 of Application 10/522,553 ('553) claims X as C<sub>1</sub>-C<sub>5</sub> alkylene which is equivalent to the elected Y as -C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>- of the instant application. Copending claim 1 of '553 claims Y as NR<sup>3</sup>CO wherein R<sup>3</sup> is hydrogen which is equivalent to the elected -NR<sup>2</sup>CO- wherein R<sup>2</sup> is hydrogen. Copending claim 1 of '553 claims R<sup>2</sup> as heteroaryl which is equivalent to the elected Z moiety as heteroaryl. Copending claim 1 of '553 claims R<sup>1</sup> as cyano and i=0 which is equivalent to the elected R<sup>1</sup> as cyano and m=0 respectively. Since instant claim 1 includes the elected criteria that X is CH, the five carbon ring fused to tetrahydroquinoline of the instant claim 1 contains a double bond that is claimed by Hanada et al. as functionally equivalent to a single bond at the same position (see formula (I) of claim 1, column 36).

This is a provisional obviousness-type double patenting rejection.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 11 through 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of androgen receptor-linked bone tissue conditions, does not reasonably provide enablement for the prevention and treatment of all androgen receptor-linked diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 11 through 13, while being enabling for treating specific diseases, does not reasonably provide enablement for preventing diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the elected Group IV compounds such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or

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guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before symptoms occur. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The paragraphs of page 24, lines 6 and 22 lists the diseases that Applicant intends to treat. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical medicine and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become afflicted before the fact. 6) The artisan using Applicants invention would be a Board Certified physician in internal medicine with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of the subject diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, In re Ferens, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, Genentech vs. Novo Nordisk, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent the subject diseases generally. That

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is, the skill is so low that no compound effective generally against androgen receptor related disorders has ever been found let alone one that can prevent such conditions.

7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by formula I with respect to the elected Group IV subject matter.

7. Furthermore, the compounds of formula I are not enabled to treat all androgen receptor-linked diseases, as claimed in claims 12 and 13. This is clearly indicated in the instant disclosure on page 4, lines 6 and 10 where Applicant cites that "...globally recognized compounds are yet to be created" and "...no such compounds are yet to be created". These statement demonstrates clearly that the mechanism is by no means definite if the compounds affecting androgen receptor-linked diseases are not yet know. This makes it quite obvious that further research effort would be needed to establish and confirm the treatments. Literature (or the lack thereof) within the relevant art also supports this uncertainty, where only a single reference in support of a quinoline derivative (a quinolin-2-one) having anabolic effects on bone and muscle, as well as activity in a sexual behavior model. Miner et al. make reference to possible quinoline derivative activity stating "...nonsteroidal selective androgen receptor modulators may be useful therapeutics for enhancing muscle, bone, and sexual function." This

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statement demonstrates clearly that the mechanism is by no means definite, and that further research effort would be needed to establish and confirm the treatments.

As discussed above and confirmed by the literature, the amount of experimentation needed to confirm and clearly establish the compounds of formula (I) as treatments for all the androgen receptor-linked conditions listed in claims 12 and 13 is considerable. Consistent with this fact is the lack of disclosed direction and guidance for establishing such links and the development of an actual treatment. Disclosed working examples stop at the androgen receptor binding activity, and failed to establish the desired link between androgen receptor activity and all the diseases of the disclosure. The nature of the invention does not support such a broad range of treatable disorders as clearly narrowly perused by the experts in the field practiced in the art. With a dependence on treatment side effects such as adverse effects to the prostate, much uncertainty would be considered a feature of the invention, and therefore a substantial level of unpredictability.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 11 through 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 11 through 13 recite the phrase "treat those diseases" which renders the claim indefinite because it is unclear whether the limitations preceding the phrase are part of the claimed invention. See MPEP § 2173.05(d). "Those" is a term generally

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used for counterdistiction contrasting with something currently applicable or near. The Examiner suggest applicant us more standard terms such as "treat said diseases".

Claim 11 drawn to a method of preventing or treating waisting disease or osteoporosis is rejected based on the lack of clarity with respect to "wasting disease". The disclosure indicates a group of conditions as "wasting diseases", however claim 11 is drawn to treating "wasting disease" in the singular. This claim should appropriately specify the specific condition that constitutes the wasting disease for which treatment is enabled.


11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David E. Gallis whose telephone number is 571-272-9068. The examiner can normally be reached on Mon-Fri 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO

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